

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 March 2005 (10.03.2005)

PCT

(10) International Publication Number
WO 2005/020985 A1

(51) International Patent Classification⁷: A61K 31/404, C07D 403/12, 413/12, A61P 3/12

(74) Agent: ASTRAZENECA; Global Intellectual Property, S-151 85 Sodertalje (SE).

(21) International Application Number:
PCT/GB2004/003620

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 25 August 2004 (25.08.2004)

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0320242.1 29 August 2003 (29.08.2003) GB
0401800.8 28 January 2004 (28.01.2004) GB

(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (for US only): BENNETT, Stuart, Norman, Lile [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

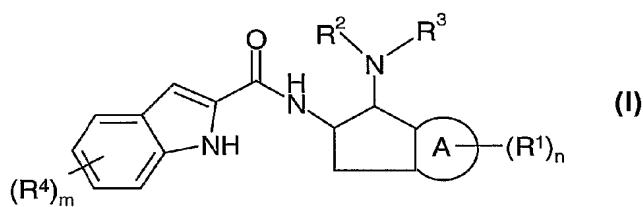
SIMPSON, Iain [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INDOLAMIDE DERIVATIVES WHICH POSSESS GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY



(57) Abstract: A compound of the formula (1) or a pharmaceutically-acceptable salt, or pro-drug thereof; wherein: A is phenylene or heteroarylene; n is 0, 1 or 2; m is 0, 1 or 2; R' is for example selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, N-(1-4C)alkylcarbamoyl, N-(1-4C)alkylsulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, (14C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, and -NHSO2(14C)alkyl; or, when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N; R² and R³ together with the nitrogen to which they are attached form an optionally substituted 4- to 7-membered, heterocyclic ring; and R⁴ is for example halo or (1-4C)alkyl; possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of compounds and pharmaceutical compositions containing them are described.

WO 2005/020985 A1

**INDOLAMIDE DERIVATIVES WHICH POSSESS GLYCOGEN
PHOSPHORYLASE INHIBITORY ACTIVITY**

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and in-vivo hydrolysable esters thereof. These heterocyclic amides possess 5 glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods of treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of 10 medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to 15 maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., et al, (1992) Diabetes Care 15; 318 - 355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

20 Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) Lancet 348, 1657-1658; Coutinho, M. et al (1999) Diabetes Care 22; 233-240; Shaw, J.E. et al (2000) Diabetes Care 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); the 25 reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 DM.

It has been estimated that, after an overnight fast, 74% of HGO was derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al 30 (1997) Am J Physiol, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues such as muscle and neuronal tissue.

Liver glycogen phosphorylase activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetologia 43, 589-597).

Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP91149 and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) *J Med Chem* 41, 2934-8; Martin et al (1998) *PNAS* 95, 1776-81). Additionally, plasma glucose concentration is reduced, in a dose related manner, db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of such agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose following a glucagon challenge were reduced significantly (Shiota et al, (1997), *Am J Physiol*, 273: E868).

The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

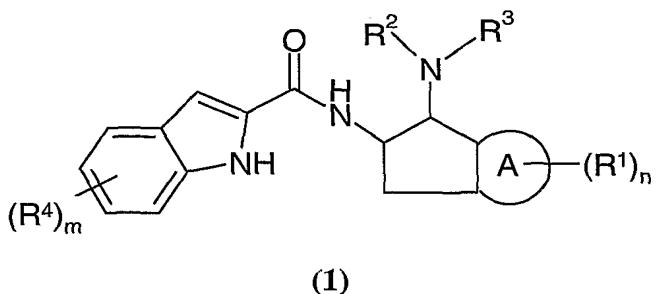
Our patent application WO 02/20530 discloses a spectrum of active glycogen phosphorylase inhibitors, amongst which are a very limited number of amino-indan containing compounds.

Our co-pending patent applications PCT/GB03/00883 and PCT/GB03/00875 disclose a variety of substituted amino-indan glycogen phosphorylase inhibitors, generally containing only one substituent on the nitrogen of the amino-indan moiety, although a number are disubstituted and contain an N-acetyl group as one substituent.

Surprisingly, we have found that a group of N-disubstituted amino-indans have physical properties (for example solubility, plasma-protein binding) and/or improved pharmacokinetic properties and/or demonstrate greater pharmacological selectivity in comparison with that of the compounds previously disclosed, which are particularly beneficial for a pharmaceutical.

According to one aspect of the present invention there is provided a compound of formula (1):

- 3 -



wherein:

A is phenylene or heteroarylene;

5 n is 0, 1 or 2;

m is 0, 1 or 2;

R¹ is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-((1-4C)alkyl)₂carbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-((1-4C)alkyl)₂sulphamoyl, -S(O)_b(1-4C)alkyl (wherein b is 0,1,or

10 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C) alkanoyl, (1-4C) alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and -NHSO₂(1-4C)alkyl;

or, when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2

15 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

R² and R³ together with the nitrogen to which they are attached form a 4- to 7-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O,

20 O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl,

(1-4C)alkoxy, (1-4C) alkanoyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2),

25 hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, and imidazolylmethyl.

R⁴ is independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl,

(2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C) alkanoyl;

or a pharmaceutically acceptable salt or pro-drug thereof;

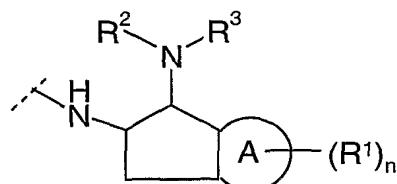
provided that the compound of formula (1) is not:

5-chloro-*N*-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

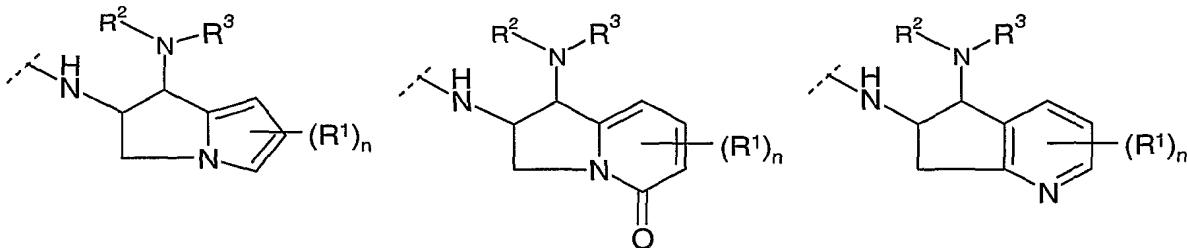
In another aspect of the invention, there is provided a compound of formula (1) as

5 hereinbefore defined, or a pharmaceutically acceptable salt or pro-drug thereof, wherein the ring comprising R^2 and R^3 together with the nitrogen to which they are attached is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl-.

It is to be understood that when A is heteroarylene, the bridgehead atoms joining ring A to the ring may be heteroatoms. Therefore, for example, the definition of



15 when A is heteroarylene encompasses the structures:



It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain.

20 In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are in-vivo hydrolysable esters of compounds of formula (1). Therefore in another aspect, the 25 invention relates to compounds of formula (1) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically 5 active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of the formula (1) 10 or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can 15 represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to 20 be understood that the invention encompasses all such solvated forms which have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

25 The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the 30 compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with

sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are 5 sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or 10 tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or 15 substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- 25 d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the 30 human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl

esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

5 Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups
10 for hydroxy include (1-10C)alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-((1-4C))alkylcarbamoyl and *N*-(di-((1-4C))alkylaminoethyl)-*N*-((1-4C))alkylcarbamoyl (to give carbamates); di-((1-4C))alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, ((1-
15 4C))alkylaminomethyl and di-((1-4C))alkylaminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in-vivo* hyrolysable esters include, for example, $R^A C(O)O((1-6C))alkyl-CO-$, wherein R^A is for example, benzyloxy-((1-4C))alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-((1-4C))piperazino-((1-
20 4C))alkyl, piperazino-((1-4C))alkyl and morpholino(1-4C)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain 25 alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl and examples of "(1-6C)alkyl" include the examples of "(1-4C)alkyl" and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example "(2-4C)alkenyl" includes vinyl, allyl and 1-propenyl and examples of "(2-
30 6C)alkenyl" include the examples of "(2-4C)alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "(2-4C)alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of

“C₂₋₆alkynyl” include the examples of “(2-4C)alkynyl” and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term “hydroxy(1-4C)alkyl” includes hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl and hydroxybutyl. The term “hydroxy(1-4C)alkyl” also 5 includes hydroxycyclopropyl and hydroxycyclobutyl. The term “hydroxyethyl” includes 1-hydroxyethyl and 2-hydroxyethyl. The term “hydroxypropyl” includes 1-hydroxypropyl, 2-hydroxypropyl and 3-hydroxypropyl and an analogous convention applies to terms such as hydroxybutyl. The term “dihydroxy(2-4C)alkyl” includes dihydroxyethyl, dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl. The term “dihydroxypropyl” includes 2,3-10 dihydroxypropyl and 1,3-dihydroxypropyl. An analogous convention applies to terms such as dihydroxyisopropyl and dihydroxybutyl. The term dihydroxy(2-4C)alkyl is not intended to include structures which are geminally disubstituted and thereby unstable.

The term “halo” refers to fluoro, chloro, bromo and iodo. The term “dihalo(1-4C)alkyl” includes difluoromethyl and dichloromethyl. The term “trihalo(1-4C)alkyl” 15 includes trifluoromethyl.

Examples of “(1-4C)alkoxy” include methoxy, ethoxy, propoxy and isopropoxy. Examples of “(1-6C)alkoxy” include the examples of “(1-4C)alkoxy” and additionally butyloxy, *t*-butyloxy, pentoxy and 1,2-(methyl)₂propoxy. Examples of “(1-4C)alkanoyl” include formyl, acetyl and propionyl. Examples of “(1-6C)alkanoyl” include the example of 20 “(1-4C)alkanoyl” and additionally butanoyl, pentanoyl, hexanoyl and 1,2-(methyl)₂propionyl. Examples of “(1-4C)alkanoyloxy” are formyloxy, acetoxy and propionoxy. Examples of “(1-6C)alkanoyloxy” include the examples of “(1-4C)alkanoyloxy” and additionally butanoyloxy, 25 pentanoyloxy, hexanoyloxy and 1,2-(methyl)₂propionyloxy. Examples of “N-((1-4C)alkyl)amino” include methylamino and ethylamino. Examples of “N-((1-6C)alkyl)amino” include the examples of “N-((1-4C)alkyl)amino” and additionally pentylamino, hexylamino and 3-methylbutylamino. Examples of “N,N-((1-4C)alkyl)₂amino” include *N*-*N*-(methyl)₂amino, *N*-*N*-(ethyl)₂amino and *N*-ethyl-*N*-methylamino. Examples of “N,N-((1-6C)alkyl)₂amino” include the example of “N,N-((1-4C)alkyl)₂amino” and additionally *N*-methyl-*N*-pentylamino and *N*,*N*-(pentyl)₂amino. Examples of “N-((1-4C)alkyl)carbamoyl” 30 are methylcarbamoyl and ethylcarbamoyl. Examples of “N-((1-6C)alkyl)carbamoyl” are the examples of “N-((1-4C)alkyl)carbamoyl” and additionally pentylcarbamoyl, hexylcarbamoyl and 1,2-(methyl)₂propylcarbamoyl. Examples of “N,N-((1-4C)alkyl)₂carbamoyl” are *N*,*N*-(methyl)₂carbamoyl, *N*,*N*-(ethyl)₂carbamoyl and *N*-methyl-*N*-ethylcarbamoyl. Examples of

“*N,N*-((1-6C)alkyl)₂carbamoyl” are the examples of “*N,N*-((1-4C)alkyl)₂carbamoyl” and additionally *N,N*-(pentyl)₂carbamoyl, *N*-methyl-*N*-pentylcarbamoyl and *N*-ethyl-*N*-hexylcarbamoyl. Examples of “*N*-((1-4C)alkyl)sulphamoyl” are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of “*N*-((1-6C)alkyl)sulphamoyl” are the examples of “*N*-((1-4C)alkyl)sulphamoyl” and additionally *N*-pentylsulphamoyl, *N*-hexylsulphamoyl and 1,2-(methyl)₂propylsulphamoyl. Examples of “*N,N*-((1-4C)alkyl)₂sulphamoyl” are *N,N*-(methyl)₂sulphamoyl, *N,N*-(ethyl)₂sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of “*N,N*-((1-6C)alkyl)₂sulphamoyl” are the examples of “*N,N*-((1-4C)alkyl)₂sulphamoyl” and additionally *N,N*-(pentyl)₂sulphamoyl, *N*-methyl-*N*-pentylsulphamoyl and *N*-ethyl-*N*-hexylsulphamoyl. Examples of “-NHSO₂(1-4C)alkyl” include methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino and tert-butylsulfonylamino.

Examples of “cyano((1-4C)alkyl” are cyanomethyl, cyanoethyl and cyanopropyl.

Examples of “(5-7C)cycloalkyl” are cyclopentyl, cyclohexyl and cycloheptyl. Examples of “(3-8C)cycloalkyl” and “(3-7C)cycloalkyl” include “(5-7C)cycloalkyl”, cyclopropyl, cyclobutyl and cyclooctyl. Examples of “(3-6C)cycloalkyl” include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of “(3-6C)cycloalkyl(1-4C)alkyl” include cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

The term “amino(1-4C)alkyl” includes aminomethyl, aminoethyl, aminopropyl, aminoisopropyl and aminobutyl. The term “aminoethyl” includes 1-aminoethyl and 2-aminoethyl. The term “aminopropyl” includes 1-aminopropyl, 2-aminopropyl and 3-aminopropyl and an analogous convention applies to terms such as aminoethyl and aminobutyl.

Examples of “(1-4C)alkoxy(1-4C)alkyl” include methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and propoxymethyl.

Examples of “-S(O)_b(1-4C)alkyl (wherein b is 0,1 or 2)” include methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propanesulphinyl, mesyl, ethylsulphonyl, propylsulphonyl and isopropylsulphonyl.

Examples of “-(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2)” include methylthiomethyl, ethylthiomethyl, propylthioethyl, methylsulphinylmethyl, ethylsulphinylmethyl, propylsulphinylmethyl, mesylmethyl, ethylsulphonylmethyl, propylsulphonylmethyl and isopropylsulphonylmethyl.

Examples of “(1-6C)alkoxycarbonyl” include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl.

Within this specification composite terms are used to describe groups comprising more than one functionality such as -(1-4C)alkylSO₂(1-4C)alkyl. Such terms are to be 5 interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example -(1-4C)alkylSO₂(1-4C)alkyl includes -methylsulphonylmethyl, -methylsulphonylethyl, -ethylsulphonylmethyl, and -propylsulphonylbutyl.

Where optional substituents are chosen from “0, 1, 2 or 3” groups it is to be 10 understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chosen from “0, 1 or 2” groups, “0 or 1” groups and “1 or 2” groups.

“Heteroarylene” is a diradical of a heteroaryl group. A heteroaryl group is an aryl, 15 monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen. Examples of heteroarylene are oxazolylene, oxadiazolylene, pyridylene, pyrimidinylene, imidazolylene, triazolylene, tetrazolylene, pyrazinylene, pyridazinylene, pyrrolylene, thienylene and furylene.

Suitable optional substituents for heteroaryl groups, unless otherwise defined, are 1, 2 20 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylS(O)_b (wherein b is 0, 1 or 2), *N*-(1-4C)alkyl)amino and *N,N*-(1-4C)alkyl)₂amino. Further suitable optional substituents for “heteroaryl” groups are 1, 2 or 3 25 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Preferred values of A, R¹ to R⁴, m and n are as follows. Such values may be used where appropriate with any of the definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

30 In one embodiment of the invention are provided compounds of formula (1), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (1), and in a further alternative embodiment are provided

pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (1). In a further alternative embodiment are provided pro-drugs of compounds of formula (1) and in a still further alternative embodiment are provided pharmaceutically-acceptable salts of pro-drugs of compounds of formula (1).

5 In one aspect of the invention A is phenylene.

 In another aspect of the invention A is heteroarylene.

 Suitable values for A are phenylene, pyridylene, pyrimidinylene, pyrrolylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, oxadiazolylene, thienylene and furylene.

10 Further suitable values for A are phenylene, pyridylene, pyrimidinylene, pyrrolylene and imidazolylene.

 Further suitable values for A are phenylene, pyridylene and pyrimidinylene.

 Further suitable values for A are phenylene and pyridylene.

15 In one embodiment, when A is heteroarylene, there is a nitrogen in a bridgehead position. In another embodiment, when A is heteroarylene, the heteroatoms are not in bridgehead positions. It will be appreciated that the preferred (more stable) bridgehead position is as shown below:

20 In one aspect of the present invention m is 1 or 2.

 In another aspect of the invention m is 1.

 In another aspect of the invention, m is 0.

 In one aspect of the present invention R⁴ is selected from halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl.

 In one aspect of the present invention R⁴ is selected from halo and methyl.

25 In another aspect of the invention R⁴ is halo.

 In another aspect of the invention R⁴ is selected from chloro and bromo.

 In another aspect of the invention R⁴ is selected from methyl, chloro and fluoro.

 In another aspect of the invention R⁴ is selected from chloro and fluoro.

 More preferably R⁴ is chloro.

30 In one aspect of the invention n is 0 or 1.

In one aspect preferably n is 1.

In another aspect, preferably n is 0.

When n is 2, and the two R¹ groups, together with the carbon atoms of A to which they are attached, form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, conveniently such a ring is a 5 or 6 membered ring. In one embodiment, such a 5 or 6 membered ring contains two O atoms (ie a cyclic acetal). When the two R¹ groups together form such a cyclic acetal, preferably it is not substituted. Most preferably the two R¹ groups together are the group -O-CH₂-O-.

In another aspect of the present invention R¹ is selected from halo, nitro, cyano,

hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl and (1-4C)alkoxy.

In a further aspect R¹ is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, -S(O)_b(1-4C)alkyl (wherein b is 0, 1 or 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl and (1-4C)alkoxy.

In a further aspect R¹ is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, -S(O)_bMe (wherein b is 0, 1 or 2), -OS(O)₂Me, methyl and methoxy.

In a further aspect, R¹ is (1-4C)alkyl.

Preferably R¹ is selected from halo and (1-4C)alkoxy.

In another embodiment preferably R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-.

In one aspect of the invention R² and R³ together with the nitrogen to which they are attached form a 5- or 6-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl-.

In another aspect of the invention, R² and R³ together with the nitrogen to which they are attached form a 5- or 6-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected

from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-5) 4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, and imidazolylmethyl.

In one aspect of the invention R² and R³ together with the nitrogen to which they are attached form a 4-membered ring as defined hereinbefore or hereinafter.

10 In another aspect of the invention R² and R³ together with the nitrogen to which they are attached form a 5-membered ring as defined hereinbefore or hereinafter.

In another aspect of the invention R² and R³ together with the nitrogen to which they are attached form a 6-membered ring as defined hereinbefore or hereinafter.

15 In another aspect of the invention R² and R³ together with the nitrogen to which they are attached form a 7-membered ring as defined hereinbefore or hereinafter.

In one aspect of the invention R² and R³ together with the nitrogen to which they are attached form a saturated ring.

In one aspect of the invention R² and R³ together with the nitrogen to which they are attached form a partially unsaturated ring.

20 In one aspect of the invention R² and R³ together with the nitrogen to which they are attached form a unsaturated ring.

In one aspect of the invention, invention R² and R³ together with the nitrogen to which they are attached form a ring containing a carbonyl group.

25 In another aspect of the invention, the ring formed by R² and R³ together with the nitrogen to which they are attached does not contain any further heteroatoms. An example of such a ring is 2-pyrrolidonyl.

In another aspect of the invention, the ring formed by R² and R³ together with the nitrogen to which they are attached contains one further heteroatom selected from O, N and S. An example of such a ring is 3-oxazolidinonyl.

30 Suitable values for a 4-7-membered ring comprising R²-N-R³ are morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl, pyrazolyl, pyrazolinyl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl,

1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl,
 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl,
 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl,
 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl,
 5 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl,
 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl.

Suitable values for a 5- or 6-membered ring comprising R^2-N-R^3 are morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl, thiomorpholino, pyrrolinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl, pyrazolyl, pyrazolinyl, 4-oxopyridyl,
 10 2-oxopyrrolidyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl,
 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl,
 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl,
 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl,
 15 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl,
 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl.

Further suitable values for the ring comprising R^2-N-R^3 are morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl,
 20 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl,
 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl,
 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl,
 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl,
 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl,
 25 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl.

Further suitable values for the ring comprising R^2-N-R^3 are morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl,
 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl,
 30 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl,
 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl,
 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl,
 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl,

1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl.

Further suitable values for the ring comprising $R^2\text{-}N\text{-}R^3$ are morpholino, piperazinyl, 3-oxazolidinonyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl and 2-oxohexahdropyrimidinyl.

Further suitable values for the ring comprising $R^2\text{-}N\text{-}R^3$ are thiomorpholino, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 10 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl.

Further suitable values for the ring comprising $R^2\text{-}N\text{-}R^3$ are morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, 3,5-dioxidopiperidinyl, 2-oxopyrrolidyl, 15 1-oxidoisothiazolidinyl, 1,1-dioxidoisothiazolidinyl, 2-oxopiperidinyl, 2-oxohexahdropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, and 1,1-dioxido-1,2,5-thiadiazolidinyl.

20 Further suitable values for the ring comprising $R^2\text{-}N\text{-}R^3$ are 2-oxo-1,3-oxazolidin-3-yl (3-oxazolidinonyl) and 2-oxopyrrolidinyl.

Suitable values for the optional substituents for the ring comprising $R^2\text{-}N\text{-}R^3$ are 1 or 2 substituents independently selected from halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-25 4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl.

Further suitable values for the optional substituents for the ring comprising $R^2\text{-}N\text{-}R^3$ are 1 or 2 substituents independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl.

Further suitable values for the optional substituents for the ring comprising $R^2\text{-}N\text{-}R^3$ 30 are 1 or 2 substituents independently selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, and dihydroxy(2-4C)alkyl.

Further suitable values for the optional substituents for the ring comprising R^2 -N- R^3 are 1 or 2 substituents independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino(1-4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl.

Further suitable values for the optional substituents for the ring comprising R^2 -N- R^3 are 1 or 2 substituents independently selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, and -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2).

Further suitable values for the optional substituents for the ring comprising R^2 -N- R^3 are 1 or 2 substituents independently selected from hydroxy, hydroxymethyl, aminomethyl, imidazolyl, methylsulfonylmethyl and methylsulfinylmethyl.

Further suitable values for the optional substituents for the ring comprising R^2 -N- R^3 are 1 or 2 substituents independently selected from hydroxy and hydroxymethyl.

In one aspect, the ring comprising R^2 -N- R^3 is substituted with one substituent selected from any of the suitable values for such substituents mentioned hereinbefore. In another aspect, the ring comprising R^2 -N- R^3 is unsubstituted.

In one aspect of the invention is provided a compound of the formula (I) wherein A is phenylene;

n is 0, 1 or 2;

m is 0, 1 or 2;

R^4 is halo;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-; R^2 and R^3 together with the nitrogen to which they are attached form a 5- or 6-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl-; or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof; provided that the compound of formula (1) is not:

5-chloro-N-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

In one aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

5 n is 0, 1 or 2;

m is 1 or 2;

R⁴ is chloro, fluoro or methyl;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a 5- or 6-membered, 10 saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, 15 carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, and imidazolylmethyl; or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof; provided that the compound of formula (1) is not:

20 5-chloro-N-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is heteroarylene;

25 n is 0, 1 or 2;

m is 0, 1 or 2;

R⁴ is halo;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a 5- or 6-membered, 30 saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from

halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl-;

5 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof;
provided that the compound of formula (1) is not:

5-chloro-N-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

In another aspect of the invention is provided a compound of the formula (I) wherein

10 A is heteroarylene;

n is 0, 1 or 2;

m is 1 or 2;

R⁴ is chloro, fluoro or methyl;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

15 R² and R³ together with the nitrogen to which they are attached form a 4- to 7-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from

20 halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, and imidazolylmethyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof;

25 provided that the compound of formula (1) is not:

5-chloro-N-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

30 n is 0, 1 or 2;

m is 0, 1 or 2;

R⁴ is halo;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a ring selected from morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl, pyrazolyl, pyrazolinyl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,

5 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,

10 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl;

15 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

n is 0, 1 or 2;

20 m is 1 or 2;

R⁴ is chloro, fluoro or methyl;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a ring selected from morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl, pyrazolyl, pyrazolinyl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,

25 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,

30 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and

1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, and 5 dihydroxy(2-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein A is heteroarylene;

n is 0, 1 or 2;

10 m is 0, 1 or 2;

R⁴ is halo;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a ring selected from morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl,

15 thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl, pyrazolyl, pyrazolinyl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,

20 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl,

25 trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylNH(1-4C)alkyl-, and di[(1-4C)alkyl]N(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

30 A is heteroarylene;

n is 0, 1 or 2;

m is 1 or 2;

R⁴ is chloro, fluoro or methyl;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;
 R^2 and R^3 together with the nitrogen to which they are attached form a ring selected from morpholino, pyrrolyl, piperazinyl, triazolyl, tetrazolyl, imidazolyl, 3-oxazolidinonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-2-yl,
5 pyrazolyl, pyrazolinyl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,
10 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), halo, cyano, fluoromethyl, 15 difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, and dihydroxy(2-4C)alkyl;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein A is phenylene;

20 n is 0, 1 or 2;

m is 0, 1 or 2;

R^4 is chloro;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

R^2 and R^3 together with the nitrogen to which they are attached form a morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazinanyl, 1-oxido-1,2,6-thiadiazinanyl and

1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl;

5 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein A is phenylene;

n is 0, 1 or 2;

m is 1 or 2;

10 R^4 is chloro, fluoro or methyl;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

R^2 and R^3 together with the nitrogen to which they are attached form a morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,

15 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl,

1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,

2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,

2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,

2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,

20 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and

1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino(1-

4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl; or a pharmaceutically acceptable salt or in-vivo

25 hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

n is 0, 1 or 2;

m is 0, 1 or 2;

30 R^4 is chloro;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

R^2 and R^3 together with the nitrogen to which they are attached form a

morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl,

3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,
1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl,
1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,
2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,
5 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,
2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,
1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and
1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents
10 independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl,
and dihydroxy(2-4C)alkyl;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein
A is phenylene;

n is 0, 1 or 2;

15 m is 1 or 2;

R⁴ is chloro, fluoro or methyl;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a
morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl,

20 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,
1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl,
1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,
2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,
2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,

25 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,
1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and
1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents
independently selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, and
-(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2);
30 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

n is 0, 1 or 2;

m is 1 or 2;

R⁴ is chloro;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a

5 morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl,
3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,
1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl,
1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,
2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,
10 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,
2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,
1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and
1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents
independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl,
15 and dihydroxy(2-4C)alkyl;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

n is 0, 1 or 2;

20 m is 1;

R⁴ is chloro, fluoro or methyl;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

R² and R³ together with the nitrogen to which they are attached form a

morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl,
25 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl,
1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl,
1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,
2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,
2,2-dioxido-1,2,3-oxathiazinanyl, 2-oxido-1,2,3-oxathiazinanyl,
30 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,
1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and

1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 substituent selected from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, and -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2);

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

5 In another aspect of the invention is provided a compound of the formula (I) wherein A is phenylene;

n is 0;

m is 0 or 1;

R⁴ is chloro;

10 R² and R³ together with the nitrogen to which they are attached form a morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl,

15 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl, 2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl, 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl, 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and 1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 or 2 substituents

20 independently selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

A is phenylene;

25 n is 0;

m is 1;

R⁴ is chloro, fluoro or methyl;

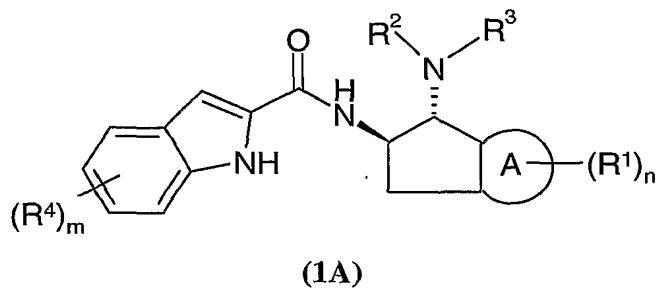
R² and R³ together with the nitrogen to which they are attached form a morpholino, piperazinyl, 3-oxazolidinonyl, thiomorpholino, homopiperazinyl, 3,5-dioxidopiperidinyl, 3-oxopyrazolin-2-yl, 4-oxopyridyl, 2-oxopyrrolidyl, 2-oxoazetidinyl, 1-oxidoisothiazolidinyl, 1-oxido-1,2-thiazinanyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-1,2-thiazinanyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoimidazolidinyl, 2-oxohexahydropyrimidinyl, 2-oxido-1,2,3-oxathiazolidinyl,

2,2-dioxido-1,2,3-oxathiazolidinyl, 2-oxido-1,2,3-oxathiazinanyl,
 2,2-dioxido-1,2,3-oxathiazinanyl, 1-oxido-1,2,5-thiadiazolidinyl,
 1,1-dioxido-1,2,5-thiadiazolidinyl, 1-oxido-1,2,6-thiadiazinanyl and
 1,1-dioxido-1,2,6-thiadiazinanyl; which ring is optionally substituted by 1 substituent selected
 5 from hydroxy, hydroxy(1-4C)alkyl, amino(1-4C)alkyl, imidazolyl, and -(1-4C)alkylS(O)_b(1-
 4C)alkyl (wherein b is 1 or 2);
 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein
 A is phenylene;

10 n is 0;
 m is 1;
 R⁴ is chloro, fluoro or methyl;
 R² and R³ together with the nitrogen to which they are attached form a
 3-oxazolidinonyl or 2-oxopyrrolidinyl ring which ring is optionally substituted by 1
 15 substituent selected from hydroxy, hydroxymethyl, aminomethyl, imidazolyl,
 methylsulfonylmethyl and methylsulfinylmethyl;
 or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

Preferred compounds of the invention are of the formula (1A), wherein R¹ to R⁷ and n
 20 are as defined in any aspect or embodiment described hereinbefore or hereinafter.

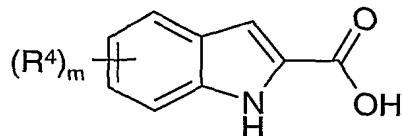


Particular compounds of the invention are each of the Examples or a pharmaceutically
 25 acceptable salt or pro-drug thereof, each of which provides a further independent aspect of the
 invention. In a further aspect of the invention there is provided any two or more of the
 Examples or a pharmaceutically acceptable salt or pro-drug thereof.

Another aspect of the present invention provides a process for preparing a compound
 30 of formula (1) or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof

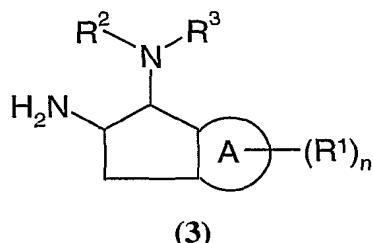
which process (wherein A, R¹ to R⁴, m and n are, unless otherwise specified, as defined in formula (1)) comprises of:

a) reacting an acid of the formula (2):



5 (2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

10 i) converting a compound of the formula (1) into another compound of the formula (1);
 ii) removing any protecting groups;
 iii) forming a pharmaceutically acceptable salt or in-vivo hydrolysable ester.

Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (2) and amines of formula (3) may be coupled

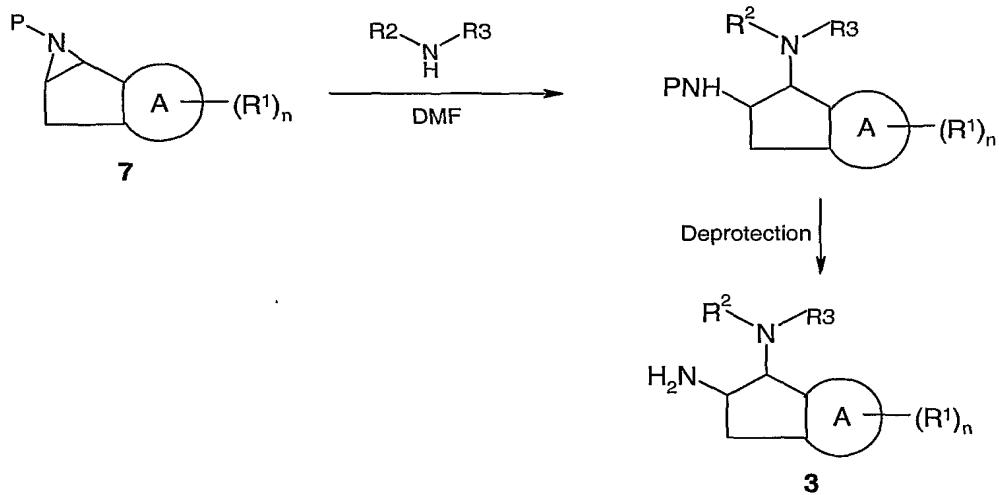
15 together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or
 20 2,6-di-alkyl-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

25 Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those

described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

The acids of formula (2) are commercially available or they are known compounds or they are prepared by processes known in the art.

5 Compounds of formula (3) may be prepared according to Scheme 3: (wherein P is a protecting group such as tert-butyloxycarbonyl (Boc), p-toluenesulfonate (tosylate) or methanesulfonate (mesylate) group).

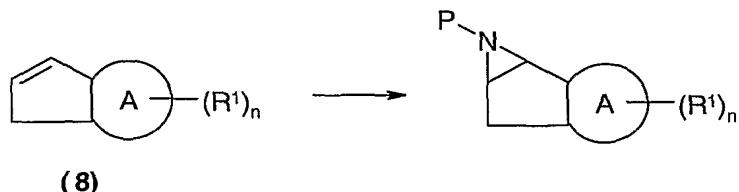


Scheme 1

10 Compounds of formula R²-NH-R³ are commercially available or they are known compounds or they are prepared by processes known in the art.

Compounds of the formula (7) may be made, for example, starting from olefins of formula (8), subjection of the olefin to aziridination would result in the suitably protected aziridine (7) in which P is H or a suitable protecting group.

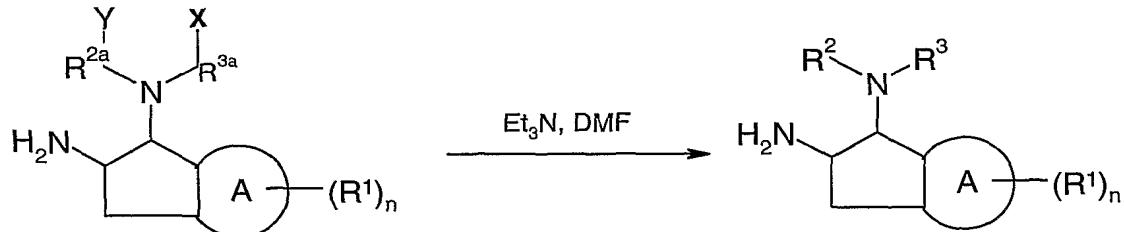
15



20 Alternatively, compound of formula (3) may be prepared by the cyclisation of a group R^{2a}-Y, (wherein Y is a nucleophile such as OH, NH₂ or SH, and R^{2a} is a group such as (1-3C)alkylsulfonyl, (1-3C)alkylcarbonyl or (1-3C)alkyl, optionally substituted by any of the optional substituents for the ring defined by R²-N-R³ or by a carbonyl or sulfonyl group) with a group R^{3a}-X (wherein X is a leaving group such as F, Cl, Br, mesylate or tosylate, and R^{3a} is

- 29 -

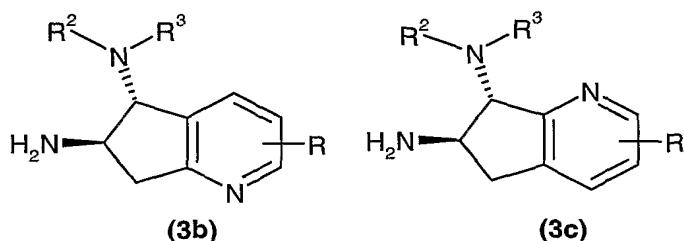
a group such as (1-3C)alkylsulfonyl, (1-3C)alkylcarbonyl or (1-3C)alkyl, optionally substituted by any of the optional substituents for the ring defined by R^2-N-R^3 or by a carbonyl or sulfonyl group), as shown in Scheme 2.



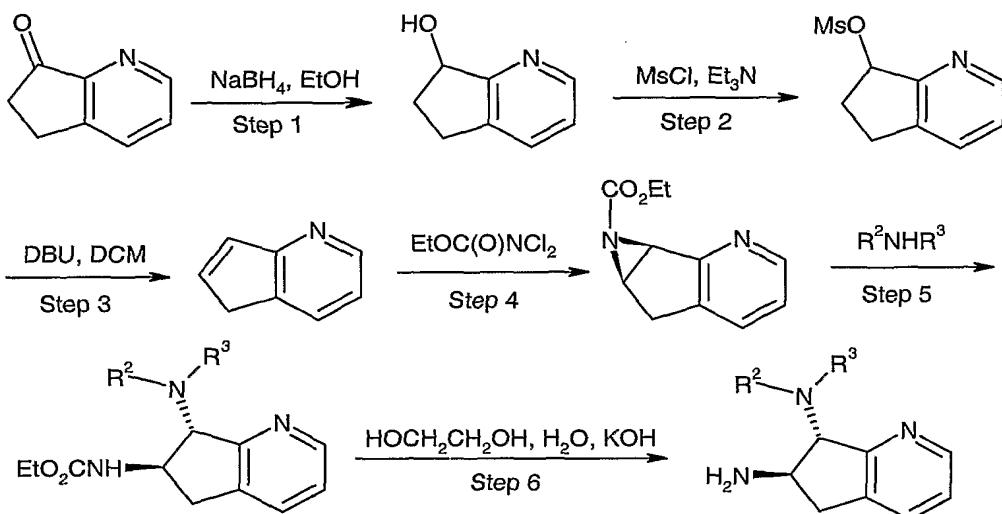
5

Scheme 2

Compounds of the formula (3) where $r = 1$ and wherein A is heteroarylene can be prepared from suitably functionalised cycloalkyl fused heterocycles. For example, when A is pyridine,



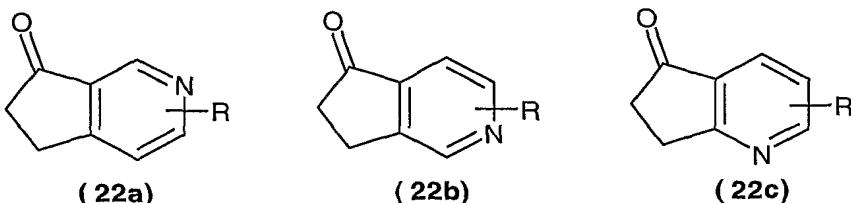
10 compounds of formula (3b) and (3c) may be prepared from the corresponding azaindanone regiosomer according to Scheme 3 :-



Scheme 3

15 Steps 1, 2, 3, 4, 5 and 6 are known in the literature or they are standard transformation known in the art. The regiosomeric azaindanones (22a, 22b, 22c) are known in the literature

or they are prepared by processes known in the art. It will be appreciated that starting from these alternative azaindanones will give rise to the regioisomeric pyridyl products.



The process described above and shown in Scheme 3 may also be applied to other six-membered heterocycles containing more than one nitrogen.

It will be appreciated that, in a similar manner, compounds of the formula (3) wherein A is heteroarylene containing a bridgehead nitrogen can be prepared from the appropriate suitably functionalised cycloalkyl fused heterocycles.

10 It will be appreciated that certain of the various ring substituents in the compounds of the present invention, for example R¹ may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions may convert one compound of the formula (1)

15 into another compound of the formula (1). Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using

20 concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group.

25 Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those

skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

5 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an 10 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

15 20 A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by 25 hydrogenation over a catalyst such as palladium-on-carbon.

30 A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

5 The thermodynamic solubility data for the compounds of the invention as given above may be measured by agitating the compound in 0.1 M phosphate at pH7.4 for 24hours, then analysis of the supernatant (for example by LCUV/MS) using a solution (for example in DMSO) of known concentration as the calibrant.

10 Plasma Protein binding may be measured using an equilibrium dialysis technique, whereby compound is added to 10% plasma giving a concentration of 20 μ M and dialysed with isotonic buffer for 18 hours at 37°C. The plasma and buffer solutions are analysed using LCUVMS and the first apparent binding constant for the compound derived. The binding constant is then used to determine the % free in 100% plasma.

15 The binding constant derived from the dialysis experiment is based upon a model of 1:1 binding between compound and albumin.



$$K1 = \frac{[PD]}{[P] \times [D]}$$

where P = free protein, D = free drug, PD = drug protein complex, K1 = first apparent binding constant.

20 As stated hereinbefore the compounds defined in the present invention possesses glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

25 The activity of the compounds is determined by measuring the inhibitory effect of the compounds on glycogen degradation, the production of glucose-1-phosphate from glycogen is monitored by the multienzyme coupled assay, as described in EP 0 846 464 A2, general method of Pesce et al (Pesce, M A, Bodourian, S H, Harris, R C, and Nicholson, J F (1977) Clinical Chemistry 23, 1171 - 1717). The reactions were in 384well microplate format in a volume of 50 μ l. The change in fluorescence due to the conversion of the co-factor NAD to

NADH is measured at 340nM excitation, 465nm emission in a Tecan Ultra Multifunctional Microplate Reader. The reaction is in 50mM HEPES, 3.5mM KH₂PO₄, 2.5mM MgCl₂, 2.5mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 8mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution. Human 5 recombinant liver glycogen phosphorylase α (hrl GP α) 20nM is pre-incubated in assay buffer solution with 6.25mM NAD, 1.25mg type III glycogen at 1.25 mg ml⁻¹ the reagent buffer, for 30 minutes. The coupling enzymes, phosphoglucomutase and glucose-6-phosphate dehydrogenase (Sigma) are prepared in reagent buffer, final concentration 0.25Units per well. 20 μ l of the hrl GP α solution is added to 10 μ l compound solution and the reaction started 10 with the addition of 20 μ l coupling enzyme solution. Compounds to be tested are prepared in 10 μ l 5% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP α is measured in the presence of 10 μ l 5% DMSO in assay 15 buffer solution and maximum inhibition measured in the presence of 5mgs ml⁻¹ N-ethylmaleimide. After 6 hours at 30°C Relative Fluorescence Units (RFUs) are measured at 340nM excitation, 465nm emission .

The assay is performed at a test concentration of inhibitor of 10 μ M or 100 μ M. Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC₅₀, a concentration predicted to inhibit the enzyme reaction by 50%.

20 Activity is calculated as follows:-

% inhibition = (1 - (compound RFUs - fully inhibited RFUs)/ (non-inhibited rate RFUs - fully inhibited RFUs)) * 100.

25 Typical IC₅₀ values for compounds of the invention when tested in the above assay are in the range 100 μ M to 1nM. Compounds of the Examples typically have IC₅₀ values of less than 10 μ M. For example, Example 2 gave an IC₅₀ value of 0.47 μ M.

The inhibitory activity of compounds was further tested in rat primary hepatocytes. Rat hepatocytes were isolated by the collagenase perfusion technique, general method of Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Cells were cultured on Nunclon six well culture plates in DMEM (Dulbecco's Modified Eagle's Medium) with high level of 30 glucose containing 10% foetal calf serum, NEAA (non essential amino acids), Glutamine, penicillin /streptomycin ((100units/100ug)/ml) for 4 to 6 hours. The hepatocytes were then cultured in the DMEM solution without foetal calf serum and with 10nM insulin and 10nM dexamethasone. Experiments were initiated after 18-20 hours culture by washing the cells and

adding Krebs-Henseleit bicarbonate buffer containing 2.5mM CaCl₂ and 1% gelatin. The test compound was added and 5 minutes later the cells were challenged with 25nM glucagon. The Krebs-Henseleit solution was removed after 60 min incubation at 37°C , 95%O₂/5%CO₂ and the glucose concentration of the Krebs-Henseleit solution measured.

5 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

10 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile 15 aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

20 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. In one aspect, the compositions of the invention are in a form suitable for oral dosage.

25 Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as 30 ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium

phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, 5 methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters 10 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and 15 hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a 20 vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

25 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be 30 present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable

emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene 5 sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

10 The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a 15 solution in 1,3-butanediol.

20 Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

25 The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will 30 generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compound of formula (1) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of 5 active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The inhibition of glycogen phosphorylase activity described herein may be applied as a 10 sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example, in order to prevent, delay or treat type 2 diabetes mellitus, the compounds of the 15 present invention or their pharmaceutically acceptable salts may be administered in combination with one or more of the following agent(s):

- 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide) and 20 glucokinase activators
- 3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, GLP-1 agonists)
- 4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone); and agents with combined PPARalpha and gamma activity
- 25 5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators)
- 6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors)
- 30 8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors)
- 9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

5

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and

10 antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin)

15 and steroidal anti-inflammatory agents (eg. cortisone).

According to a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man

20 by therapy.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

5 According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

10 According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

15 According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

20 As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

25 In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

30 In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

5 (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

10 (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard,

15 determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO- δ_6) as solvent unless otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform CDCl₃;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

20 (viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is (M-H)⁻;

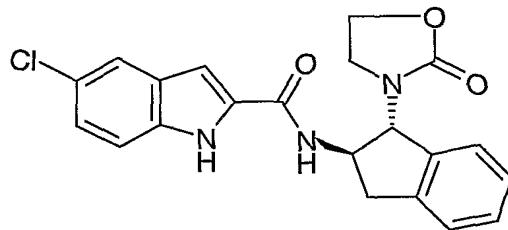
25 (xi) The following abbreviations may be used:

	SM	starting material;
	EtOAc	ethyl acetate;
30	MeOH	methanol;
	EtOH	ethanol;
	DCM	dichloromethane;
	HOBt	1-hydroxybenzotriazole;

	DIPEA	di-isopropylethylamine;
	EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride;
5	Et ₂ O	diethyl ether;
	THF	tetrahydrofuran;
	DMF	<i>N,N</i> -dimethylformamide;
	HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluroniumhexafluorophosphate
10	EDAC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
	TFA	Trifluoroacetic acid
	DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
	DMA	<i>N,N</i> -dimethylacetamide
15	NaHMDS	Sodium hexamethyldisilazide

The Examples and Intermediates were named using the "Name" module in the ACD 5.0 program suite [Advanced Chemistry Development (Toronto, Canada)]

20 **Example 1: 5-Chloro-*N*-(*1R,2R*)-1-(2-oxo-1,3-oxazolidin-3-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide**

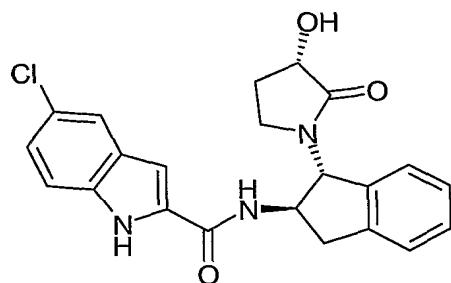


25 4-Nitrobenzyl ((1*R,2R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)(2-hydroxyethyl)carbamate (**Intermediate 1**; 160 mg, 0.29 mmol) was dissolved in anhydrous DMA (3 mL) under an argon atmosphere at 10°C. Sodium hydride ((60% w/v suspension in oil, 46 mg, 1.17 mmol) was added and the mixture allowed to warm to ambient temperature for 1hr. Water (5 mL) was added and the mixture extracted with ethyl acetate (10 mL). The organic extracts were washed with water (6x5 mL), brine, dried (MgSO₄), filtered and the volatiles were removed by evaporation under reduced pressure. The crude residues

were purified by silica chromatography (1:1, iso-hexane:ethyl acetate) to give the title compound (100 mg, 87%) as a white powder.

¹H NMR δ: 2.97 (m, 1H), 3.35 (m, 1H), 3.5 (m, 1H), 3.82 (m, 1H), 4.47 (m, 2H), 4.97 (m, 1H), 5.58 (d, 1H), 6.8 (d, 1H), 7.17 (m, 6H), 7.43 (s, 1H), 7.72 (d, 1H), 9.25 (s, 1H); MS m/z 5 394, 396 (M-H).

Example 2: 5-Chloro-N-[(1R,2R)-1-[(3S)-3-hydroxy-2-oxopyrrolidin-1-yl]-2,3-dihydro-1H-inden-2-yl]-1H-indole-2-carboxamide



10 (3S)-1-[(1R,2R)-2-Amino-2,3-dihydro-1H-inden-1-yl]-3-hydroxypyrrolidin-2-one
(Intermediate 9; 116 mg, 0.5 mmol), 5-chloroindole-2-carboxylic acid (98 mg, 0.5 mmol), DIPEA (86 uL, 0.5 mmol) and HOBr (68 mg, 0.5 mmol) were dissolved in DMA (2 mL). EDCI (120 mg, 0.63 mmol) was added and the reaction mixture stirred at ambient temperature for 24 h. Water (20 mL) was added and the resulting precipitate was filtered.

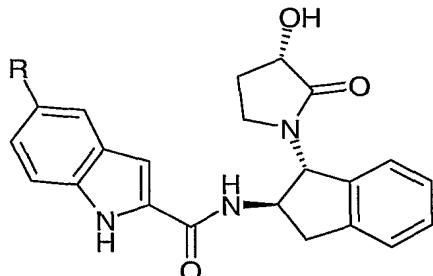
15 The crude material was purified by flash column chromatography (SiO₂, eluent: 1:1, isohexane:EtOAc to EtOAc) to afford the title compound (160 mg, 78%) as a white solid.
¹H NMR δ: 1.75 (m, 1H), 2.28 (m, 1H), 3.05 (m, 2H), 3.22 (dd, 1H), 3.39 (dd, 1H), 4.07 (m, 1H), 4.81 (m, 1H), 5.58 (2H, m), 7.01 (d, 1H), 7.11 (s, 1H), 7.18 (dd, 1H), 7.23 (m, 3H), 7.41 (d, 1H), 7.71 (s, 1H), 8.87 (d, 1H), 11.77 (br s, 1H). MS m/z 408/410 [M-H]⁻.

20 The following examples were made by the process of **Example 2**, using (3S)-1-[(1R,2R)-2-Amino-2,3-dihydro-1H-inden-1-yl]-3-hydroxypyrrolidin-2-one (**Intermediate 9**) as the amine and the appropriate commercially available carboxylic acid:

- 43 -

Example 3: 5-Fluoro-N-[(1*R*,2*R*)-1-[(3*S*)-3-hydroxy-2-oxopyrrolidin-1-yl]-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide

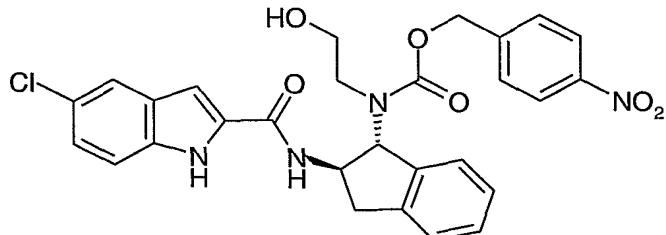
Example 4: 5-Methyl-N-[(1*R*,2*R*)-1-[(3*S*)-3-hydroxy-2-oxopyrrolidin-1-yl]-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide



5

Example No	R	¹ H-NMR δ:	MS m/z
3	F	1.75 (m, 1H), 2.29 (m, 1H), 3.05 (m, 2H), 3.19 (dd, 1H), 3.38 (dd, 1H), 4.10 (m, 1H), 4.81 (m, 1H), 5.58 (2H, m), 7.01 (m, 2H), 7.10 (s, 1H), 7.25 (m, 3H), 7.40 (m, 2H), 8.85 (d, 1H), 11.67 (br s, 1H)	392 [M-H] ⁻
4	Me	1.75 (m, 1H), 2.25 (m, 1H), 2.35 (s, 3H), 3.05 (m, 2H), 3.18 (dd, 1H), 3.40 (dd, 1H), 4.08 (dd, 1H), 4.81 (m, 1H), 5.57 (2H, m), 7.00 (m, 3H), 7.25 (m, 3H), 7.38 (s, 1H), 8.77 (d, 1H), 11.41 (br s, 1H)	388 [M-H] ⁻

Intermediate 1: 4-Nitrobenzyl ((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)(2-hydroxyethyl)carbamate



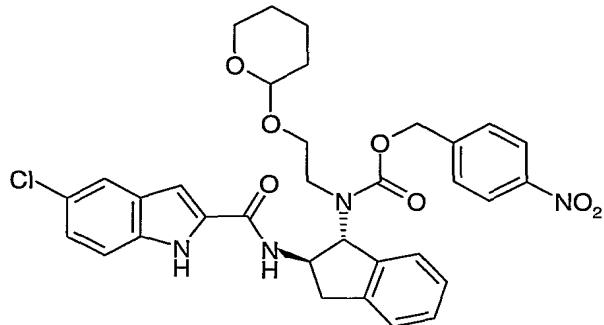
10

4-Nitrobenzyl ((1*R*,2*R*)-2-{[(5-chloro-1*H*-indol-2-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]carbamate (Intermediate 2; 250mg, 0.4mmol) was dissolved in 20% aqueous acetic acid (5 mL) and heated at 50 °C for 1.5hr. The reaction was cooled to ambient temperature, water (10 mL) added and the precipitate filtered, washed

with water and dried under vacuum at 50 °C to give the title compound (180mg, 82%) as a cream powder.

MS m/z 571, 573 (M+Na).

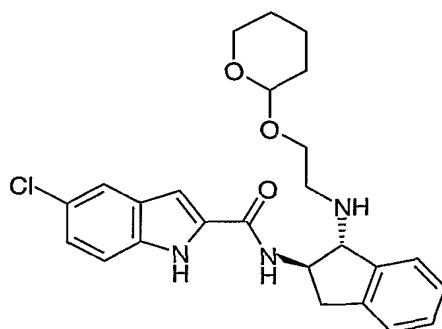
5 **Intermediate 2: 4-Nitrobenzyl ((1R,2R)-2-[(5-chloro-1H-indol-2-yl)carbonyl]amino)-2,3-dihydro-1H-inden-1-yl]2-(tetrahydro-2H-pyran-2-yloxy)ethyl]carbamate**



10 5-Chloro-N-((1R,2R)-1-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}-2,3-dihydro-1H-inden-2-yl)-1H-indole-2-carboxamide (**Intermediate 3: 454 mg, 1.0 mmol**) and anhydrous pyridine (158 mg, 2.0 mmol) was dissolved in anhydrous THF (5 mL) under an argon atmosphere at 5 °C. 4-Nitrobenzyl chloroformate (237 mg, 1.1 mmol) in anhydrous THF (2.5 mL) was added and the mixture allowed to warm to ambient temperature. The reaction mixture was diluted with ethyl acetate (25 mL) washed with water (10 mL), brine (10 mL), dried (MgSO_4), filtered and the volatiles were removed by evaporation under reduced pressure. The crude residues were purified by silica chromatography (2:1, iso-hexane:ethyl acetate) to give the title compound (250 mg, 39%) as a pale brown foam.

15 MS m/z 631, 633 (M-H).

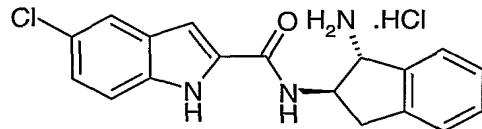
20 **Intermediate 3: 5-Chloro-N-((1R,2R)-1-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}-2,3-dihydro-1H-inden-2-yl)-1H-indole-2-carboxamide**



5 *N*-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide hydrochloride salt (**Intermediate 4**; 2.7 g, 7.45 mmol), DIPEA (2.55 mL, 14.9 mmol) and (+/-)-2-(2-iodoethoxy)tetrahydro-2*H*-pyran (CAS Reg. No.: 96388-83-9, 1.9 g, 7.45 mmol) was dissolved in DMA (20 mL) and stirred at 60 °C. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (75 mL) washed with water (6x30 mL), brine (30 mL) and dried (MgSO_4), filtered and the volatiles were removed by evaporation under reduced pressure. The crude residues were purified by silica chromatography (ethyl acetate) to give the title compound (900 mg, 26%) as a brown foam.

10 ^1H NMR (CDCl_3) δ : 1.5(m, 4H), 1.8(m, 2H), 2.85(m, 1H), 3.07(m, 2H), 3.48(m, 1H), 3.6(m, 2H), 3.9(m, 2H), 4.35(d, 1H), 4.58(m, 1H), 4.7(m, 1H), 6.6(m, 1H), 6.78(d, 1H), 7.3(m, 6H), 7.58(d, 1H), 9.9(s, 1H); MS m/z 454/456(M+H).

Intermediate 4: *N*-[(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl]-5-chloro-1*H*-indole-2-carboxamide hydrochloride



15

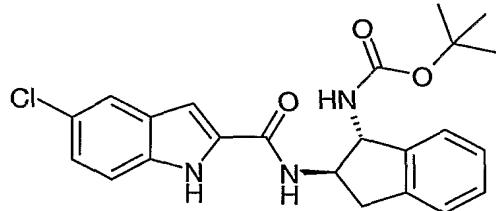
15 *tert*-Butyl ((1*R*,2*R*)-2-[(5-chloro-1*H*-indol-2-yl)carbonyl]amino)-2,3-dihydro-1*H*-inden-1-ylcarbamate (**Intermediate 5**; 4.2 g, 9.86 mmol) was dissolved in 4N HCl in dioxane (50 mL) and the mixture stirred for approximately 20 hours. Evaporation under reduced pressure followed by co-evaporation with dioxane (2 x 25 mL) and drying gave the title compound (3.0 g, 82%) as a pale brown amorphous powder.

20

1 ^1H NMR δ : 3.05 (dd, 1H), 3.4 (dd, 1H), 4.72 (m, 1H), 4.92(m, 1H), 7.19 (d, 1H), 7.3 (m, 4H), 7.45 (d, 1H), 7.72 (m, 2H), 8.86 (s, 3H), 9.33 (d, 1H), 11.95 (s, 1H); MS m/z 326, 328.

25

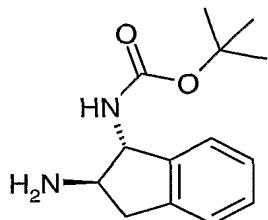
Intermediate 5: *tert*-Butyl ((1*R*,2*R*)-2-[(5-chloro-1*H*-indol-2-yl)carbonyl]amino)-2,3-dihydro-1*H*-inden-1-ylcarbamate



5-Chloroindole-2-carboxylic acid (391 mg, 2 mmol), *tert*-Butyl [(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]carbamate (**Intermediate 6**; 497 mg, 2 mmol), DIPEA (350 μ L, 2 mmol) and HOEt (270 mg, 2 mmol) were dissolved in DCM (10 mL), stirred for 5 mins, then EDCI (479mg, 2.5 mmol) was added and the reaction stirred for 3 hours. The volatiles were removed by evaporation under reduced pressure, EtOAc (25 mL) was added and the organic solution washed with water (2 x 10 mL), brine (10 mL), dried (MgSO_4) and the volatiles removed by evaporation under reduced pressure to give the title compound (800 mg, 94%) as a pale brown foam.

5 ^1H NMR δ : 1.47 (s, 9H), 2.9 (dd, 1H), 3.27 (dd, 1H), 4.7 (m, 1H), 5.25 (m, 1H), 7.24 (m, 6H), 10 7.5 (m, 2H), 7.79 (s, 1H), 8.91 (d, 1H), 11.85 (s, 1H), MS m/z 426, 428.

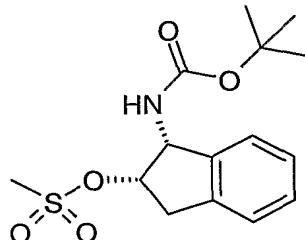
Intermediate 6: (1*R*, 2*R*)-2-Amino-1-[(1,1-dimethylethoxy)carbonylamino]indan



(1*R*, 2*S*)-1-[(1,1-Dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan
 15 (**Intermediate 7**; 18.1g, 55.3mmol) was dissolved in dry dimethyl acetamide (100 ml). Sodium azide (5.4g, 83.0mmol) was added and the mixture heated to 90°C for 6 hours. The reaction was cooled, diluted with ethyl acetate (150 ml), washed with water (6 x 200 ml) and dried over magnesium sulphate. 10% Palladium on activated carbon was added and the mixture stirred under a hydrogen atmosphere for 24 hours. Filtration through celite followed 20 by evaporation gave the title compound (2.6 g, 98%) as a white solid.

^1H NMR δ : 1.45 (s, 9H), 2.50 (dd, 1H), 3.05 (dd, 1H), 3.30 (m, 3H), 4.55 (m, 1H), 7.1 (m, 5H).

Intermediate 7: (1R, 2S)- 1-[(1,1-dimethylethoxy)carbonylamino]-2-methanesulphonyloxyindan



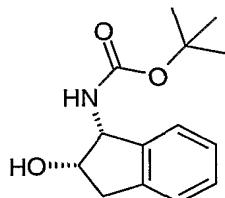
(1R, 2S)- 1-[(1,1-Dimethylethoxy)carbonylamino]-2-hydroxyindan (**Intermediate 8**; 14.0 g,

5 56.2 mmol) was dissolved in DCM (200 mL) and triethylamine (11.8 mL, 84.3 mmol).

Methanesulfonyl chloride (7.1 g, 61.9 mmol) dissolved in DCM (20 mL) was added and the mixture stirred at room temperature for 3 h. The mixture was evaporated and EtOAc (250 mL) added. After washing with water and drying over magnesium sulphate the organic solution was evaporated to afford the title compound (9.7 g, 98%) as a white solid.

10 ^1H NMR δ : 1.45 (s, 9H), 3.15 (m, 2H), 3.18 (s, 3H), 5.20 (m, 1H), 5.35 (m, 1H), 7.15 (m, 4H), 7.45 (d, 1H).

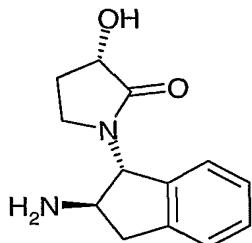
Intermediate 8: (1R, 2S)-1-[(1,1-Dimethylethoxy)carbonylamino]-2 hydroxyindan



15 (1R, 2S)-1-Amino-2-hydroxyindan (12.0g, 80.5mmol) was dissolved in DCM (500 ml) and triethylamine (22.4 ml, 161mmol). Di-*tert*-butyl dicarbonate (22.0g, 100mmol) in DCM (50 ml) was added and the mixture stirred at room temperature for 20 hours then evaporated. EtOAc (200 ml) was added, the solution washed with water, dried over magnesium sulphate and evaporated. The crude product was purified by chromatography on silica with 4:1 *iso*-hexane:EtOAc as eluent to give the title compound (17.9 g, 90%) as a white solid.

20 ^1H NMR δ : 1.42 (s, 9H), 2.78 (dd, 1H), 3.00 (dd, 1H), 4.40 (m, 1H), 4.85 (m, 1H), 4.95 (m, 1H), 6.30 (d, 1H), 7.10 (m, 4H).

Intermediate 9: (3S)-1-[(1R,2R)-2-Amino-2,3-dihydro-1H-inden-1-yl]-3-hydroxypyrrolidin-2-one

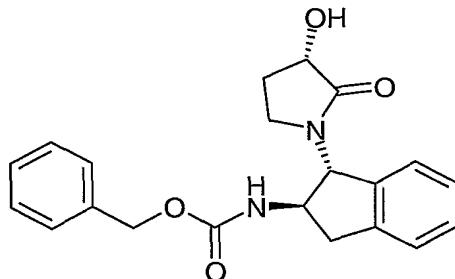


Benzyl {(1R,2R)-1-[(3S)-3-hydroxy-2-oxopyrrolidin-1-yl]-2,3-dihydro-1H-inden-2-yl}carbamate (**Intermediate 10**; 3.4 g, 9.28 mmol) and formic acid (10 mL) were suspended in EtOH (100 mL). 10% palladium on carbon was added and the reaction mixture was stirred, under an argon atmosphere, at ambient temperature for 1 h. The reaction mixture was filtered, the volatiles removed under reduced pressure and the crude product co-evaporates with toluene (3 x 75 mL). The crude material was re-dissolved in EtOH:water (60 mL, 5:1) and mesoporous carbonate resin (5 g) added and the suspension stirred at ambient temperature for 1 h. The suspension was filtered and the volatiles removed under reduced pressure to afford the title compound (1.5 g, 70%).

¹H NMR δ: 1.71 (m, 1H), 2.28 (m, 1H), 2.60 (dd, 1H), 2.87 (t, 1H), 3.02 (dd, 1H), 3.12 (dd, 1H), 3.45 (dd, 1H), 4.22 (t, 1H), 5.08 (s, 2H), 6.92 (d, 1H), 7.15 (m, 3H). MS m/z 233.

15

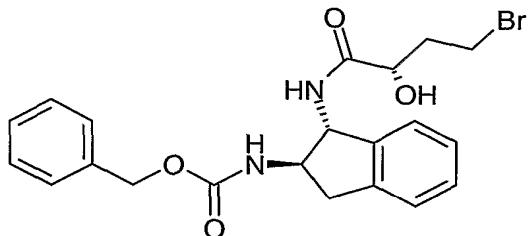
Intermediate 10: Benzyl {(1R,2R)-1-[(3S)-3-hydroxy-2-oxopyrrolidin-1-yl]-2,3-dihydro-1H-inden-2-yl}carbamate



Benzyl ((1R,2R)-1-{[(2S)-4-bromo-2-hydroxybutanoyl]amino}-2,3-dihydro-1H-inden-2-yl)carbamate (**Intermediate 11**; 5.0 g, 11.18 mmol) was dissolved in THF (100 mL) and the solution cooled to 5 °C. Sodium hexamethyldisilazide (22.4 mL, 1 M in THF, 22.4 mmol) was added dropwise and the solution warmed from 5 °C to ambient temperature and stirred at ambient temperature for 1 h. The reaction was cooled to 5 °C, saturated aqueous ammonium chloride (50 mL) added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The

combined organic phase was washed with water (100 mL), brine (100 mL), dried (MgSO_4) and the volatiles removed under reduced pressure to afford the title compound (3.95 g, 96%).
 $^1\text{H NMR}$ δ : 1.75 (m, 1H), 2.29 (m, 1H), 2.90 (m, 2H), 3.12 (dd, 1H), 3.35 (m, 1H), 4.1 (dd, 1H), 4.32 (m, 1H), 5.02 (s, 2H), 5.41 (d, 1H), 5.60 (d, 1H), 6.98 (d, 1H), 7.22 (m, 3H), 7.35 (m, 5H), 7.75 (d, 1H).

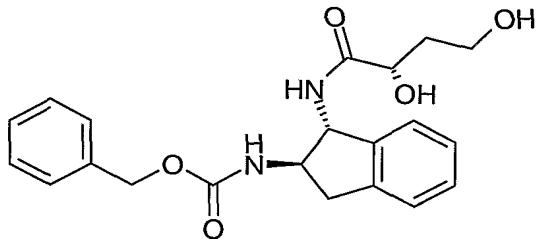
Intermediate 11: Benzyl ((1*R*,2*R*)-1-<{[(2*S*)-4-bromo-2-hydroxybutanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbamate



10

Benzyl ((1*R*,2*R*)-1-<{[(2*S*)-2,4-dihydroxybutanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbamate (**Intermediate 12**; 6.6 g, 17.2 mmol) and carbon tetrabromide (6.26 g, 18.9 mmol) were dissolved in DMA (120 mL). Polymer supported triphenylphosphine (17.2 g, 3 mmol/g polymer loading, 51.5 mmol) was added and the reaction stirred at ambient 15 temperature for 1 h. The reaction was diluted with EtOAc (350 mL) and filtered. The organic phase was washed with water (6 x 100 mL) and brine (200 mL), dried (MgSO_4) and the volatiles removed under reduced pressure. The crude material was flash column chromatography (SiO_2 , eluent: 2:1, isohexane:EtOAc to 1:2, isohexane:EtOAc) to afford the title compound (4.2 g, 55%) as a white solid.
20 $^1\text{H NMR}$ δ : 2.1 (m, 2H), 2.72 (dd, 1H), 3.10 (dd, 1H), 3.51 (dd, 2H), 4.07 (dd, 1H), 4.31 (m, 1H), 5.02 (s, 2H), 5.23 (t, 1H), 7.02 (d, 1H), 7.18 (m, 3H), 7.35 (m, 5H), 7.62 (d, 1H), 8.11 (d, 1H). MS m/z 470 $[\text{M}+\text{Na}]^+$.

Intermediate 12: Benzyl [(1R,2R)-1-[(2S)-2,4-dihydroxybutanoyl]amino]-2,3-dihydro-1H-inden-2-yl]carbamate

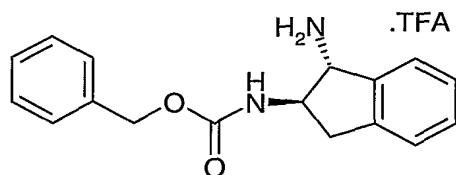


Benzyl [(1R,2R)-1-amino-2,3-dihydro-1H-inden-2-yl]carbamate trifluoroacetate

5 (Intermediate 13; 11 g, 21.4 mmol), (3S)-3-hydroxydihydrofuran-2(3H)-one (6.5 g, 42.8 mmol) and DIPEA were dissolved in 1,4-dioxane (100 mL) and the resulting solution was heated at 100 °C for 24 h. The volatiles were removed under reduced pressure and the crude material was purified by flash column chromatography (SiO₂, eluent: 1:9 isohexane:EtOAc to EtOAc) to afford the title compound (6.6%, 80%) as a white solid.

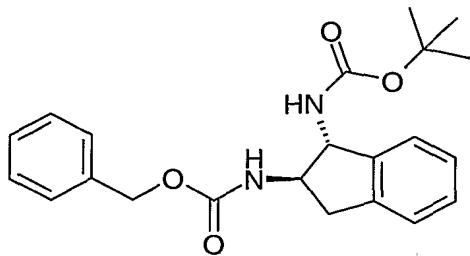
10 ¹H NMR δ: 1.61 (m, 1H), 1.85 (m, 1H), 2.72 (dd, 1H), 3.12 (dd, 1H), 3.51 (m, 1H), 4.05 (m, 1H), 4.30 (m, 1H), 4.40 (t, 1H), 5.02 (s, 2H), 5.25 (t, 1H), 5.37 (d, 1H), 7.02 (d, 1H), 7.18 (m, 3H), 7.35 (m, 5H), 7.62 (d, 1H), 8.00 (d, 1H).

Intermediate 13: Benzyl [(1R,2R)-1-amino-2,3-dihydro-1H-inden-2-yl]carbamate trifluoroacetate



15 Benzyl *tert*-butyl (1R,2R)-2,3-dihydro-1H-indene-1,2-diylbiscarbamate (Intermediate 14; 8.2 g, 21.44 mmol) was dissolved in DCM (100 mL) and TFA (20 mL) was added and the resulting solution stirred at ambient temperature for 20 h. The volatiles were removed under reduced pressure and the crude product co-evaporated with toluene (2 x 100 mL) to afford the title compound (11 g, 100%) was a pale yellow gum.

MS m/z 283

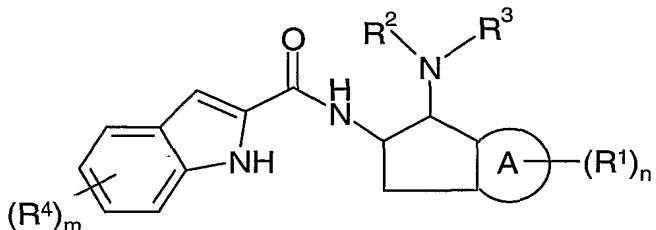
Intermediate 14: Benzyl *tert*-butyl (1*R*,2*R*)-2,3-dihydro-1*H*-indene-1,2-diylbiscarbamate

(1*R*, 2*R*)-*Trans*-2-Amino-1-[(1,1-dimethylethoxy)carbonylamino]indan (**Intermediate 6**, 7.44 g, 30 mmol) and DIPEA (7.68 mL, 45 mmol) were dissolved in DCM (150 mL) and the 5 solution cooled to 5 °C. Benzyl chloroformate (6.16 mL, 36 mmol) was added dropwise, keeping internal temperature <10 °C. After the addition was complete the reaction mixture was warmed to ambient temperature and stirred for 2 h. The reaction mixture was then washed with citric acid (100 mL), water (2 x 100 mL) and brine (100 mL). The organic phase was dried (MgSO_4), filtered and the volatiles removed under reduced pressure. The resulting 10 solid was then recrystallised from EtOAc:isohexane (2:3, 75 mL) to afford the title compound (8.2 g, 71%) as a cream powder.

^1H NMR (CDCl_3) δ : 1.50 (s, 9H), 2.71 (dd, 1H), 3.40 (dd, 1H), 4.1 (m, 1H), 4.91 (m, 1H), 5.05 (t, 1H), 5.12 (s, 2H), 5.65 (m, 1H), 7.28 (m, 9H).

Claims

1. A compound of formula (1):



5 (1)

wherein:

A is phenylene or heteroarylene;

n is 0, 1 or 2;

m is 0, 1 or 2;

10 R¹ is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-((1-4C)alkyl)₂carbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-((1-4C)alkyl)₂sulphamoyl, -S(O)_b(1-4C)alkyl (wherein b is 0,1, or 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and -NHSO₂(1-4C)alkyl;

15 or, when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

20 R² and R³ together with the nitrogen to which they are attached form a 4- to 7-membered, saturated, partially unsaturated or unsaturated heterocyclic ring optionally containing 1, 2 or 3 further heteroatoms independently selected from O, N and S (provided that there are no O-O, O-S or S-S bonds), wherein any N, S or C atom may optionally be oxidised, and wherein said heterocyclic ring is optionally substituted with 1 or 2 substituents independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, amino(1-4C)alkyl, and imidazolylmethyl.

R^4 is independently selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl; or a pharmaceutically acceptable salt or pro-drug thereof;

5 provided that the compound of formula (1) is not:

5-chloro-*N*-[(1*R*,2*R*)-1-(2,5-dioxomorpholin-4-yl)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-indole-2-carboxamide.

2. A compound of formula (1) or a pharmaceutically acceptable salt or pro-drug thereof

10 as claimed in Claim 1 wherein A is phenylene.

3. A compound of formula (1) or a pharmaceutically acceptable salt or pro-drug thereof as claimed in Claim 1 or Claim 2, wherein R^2 and R^3 together with the nitrogen to which they are attached form a 5- or 6-membered ring.

15

4. A compound of formula (1) or a pharmaceutically acceptable salt or pro-drug thereof as claimed in Claim 1, Claim 2 or Claim 3 wherein n is 0.

20

5. A compound of formula (1) or a pharmaceutically acceptable salt or pro-drug thereof as claimed in any one of the preceding claims wherein optional substituents on the ring formed by R^2 and R^3 together with the nitrogen to which they are attached are selected from halo, carboxy, (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino(1-4C)alkyl, imidazolyl, -(1-4C)alkylS(O)_b(1-4C)alkyl (wherein b is 1 or 2), hydroxy(1-4C)alkyl, and dihydroxy(2-4C)alkyl.

25

6. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

30

7. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use in a method of treatment of a warm-blooded animal such as man by therapy.

8. A compound of the formula (1), or a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester thereof, as claimed in claim 1, for use as a medicament.

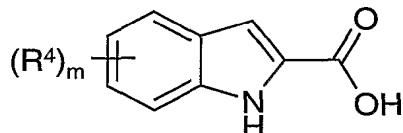
9. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in claim 1, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

10. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

11. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in-vivo* hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

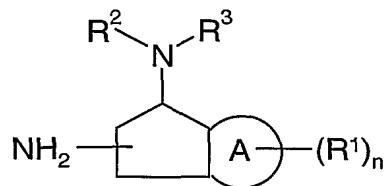
12. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

20 reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

25

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

INTERNATIONAL SEARCH REPORT

International Application No

12/GB2004/003620

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/404 C07D403/12 C07D413/12 A61P3/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 136 071 A (PFIZER PROD INC) 26 September 2001 (2001-09-26) the whole document -----	1-12
A	WO 02/20530 A (FREEMAN SUE ; KENNY PETER (GB); MORLEY ANDREW (GB); WHITTAMORE PAUL (G) 14 March 2002 (2002-03-14) page 36, line 25 – page 39, line 30; examples 112,133-140,142,148-154 -----	1-12
P,A	WO 03/074484 A (WHITTAMORE PAUL ROBERT OWEN ; SIMPSON IAIN (GB); ASTRAZENECA UK LTD (G) 12 September 2003 (2003-09-12) the whole document -----	1-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the international search report
12 October 2004	20/10/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Gavriliu, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

...:/GB2004/003620

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 1136071	A 26-09-2001	AU 2813001	A	27-09-2001
		CA 2341344	A1	22-09-2001
		EP 1136071	A2	26-09-2001
		HU 0101158	A2	28-02-2002
		JP 2001302546	A	31-10-2001
		NZ 510677	A	25-10-2002
		US 2003004162	A1	02-01-2003
		ZA 200102318	A	20-09-2002
-----	-----	-----	-----	-----
WO 0220530	A 14-03-2002	AT 263772	T	15-04-2004
		AU 8283301	A	22-03-2002
		BG 107624	A	30-01-2004
		BR 0113606	A	24-06-2003
		CA 2417594	A1	14-03-2002
		CN 1473163	T	04-02-2004
		CZ 20030616	A3	14-05-2003
		DE 60102710	D1	13-05-2004
		DK 1317459	T3	12-07-2004
		EP 1317459	A1	11-06-2003
		HU 0400784	A2	28-07-2004
		JP 2004508376	T	18-03-2004
		NO 20031024	A	05-03-2003
		NZ 524011	A	27-08-2004
		PT 1317459	T	31-08-2004
		WO 0220530	A1	14-03-2002
		SI 1317459	T1	31-08-2004
		SK 2592003	A3	05-08-2003
		US 2003232875	A1	18-12-2003
-----	-----	-----	-----	-----
WO 03074484	A 12-09-2003	WO 03074484	A1	12-09-2003
-----	-----	-----	-----	-----